IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of James T. English, et al. Art Unit 1639
Serial No. 09/829,549
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Confirmation No. 8198
For PHAGE DISPLAY SELECTION OF ANTI FUNGAL PEPTIDES
Examiner Teresa D. Wessendorf

REPLY BRIEF

Edward J. Hejlek, Reg. No. 31,525
SENNIGER POWERS
One Metropolitan Square, 16th Floor
St. Louis, Missouri 63102
(314) 231-5400

A. The Office Has Failed to Preserve the Grounds of Rejection Directed to (i) Claims 44 and 49; (ii) Claim 5; and (iii) Claims 35, 36, and 48

37 C.F.R. § 1.113 and M.P.E.P. § 706.07 require the Examiner to repeat each applicable ground of rejection in a final Office action.[1] The Examiner failed to do this. The only ground of rejection recited in the final Office action was directed to claims 1-4, 6-9, 32-34, 37-43, 45-47, and 49-51.[2] Grounds of rejection directed to claims 44 and 49, claim 5, and claims 35, 36, and 48 were not recited. Having thus failed to comply with the C.F.R. and the M.P.E.P., the Examiner is not now entitled to argue these omitted grounds of rejection. For completeness, however, Appellants have nonetheless included arguments directed to the grounds of rejection waived by the Examiner.

B. The Office Has Failed to Articulate a *Prima Facie* Case of Obviousness of the Group I Claims

Claim 1 is directed to a method for the identification of ***non-immunoglobulin peptides*** having an affinity for the surface of a fungus.

According to the Examiner, "there is nothing in the [quoted passage] of Gough et al. that indicates 'the antibodies and others identified to date' had no effect on *Phytophthora*. Rather, section [sic] discloses that the lack of response is on a preliminary assay in the sporangia **of** tomato leaf discs."[3] This assertion is patently incorrect. According to Gough et al., their approach "showed no detectable antifungal activity for any of the antibodies"[4] and they hold out a vague hope that, someday, in the indeterminate future, "other **scFvs** . . . *may well provide*" useful tools.[5] Gough et al. merely identified single-chain Fv antibodies that bind to the surface of *Phytophthora*, and admit that their antibodies and others identified to date **have had no effect on *Phytophthora* whatsoever**.[6]

Furthermore, sporangia are understood to be plant or fungal structures including spores, which form part of the life cycle of many plants, algae, and fungi. According to Gough et al., their MBP-scFv fusion proteins are ***mixed*** with sporangia ***and then used***

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[1] See Appellants' Second Amended Appeal Brief, pages 1-2.
[2] See Office action dated July 25, 2005, page 2 et seq.
[3] Examiner's Answer dated June 1, 2007, page 8-9, emphasis added.
[4] Gough et al. at 107.
[5] Id. (emphasis added)
[6] Gough et al. at 105-107.

to inoculate tomato leaf discs.[7] There is nothing to indicate that the sporangia were "of" or perhaps derived from the tomato leaf discs. Instead, this passage indicates that, when mixed with infectious sporangia (i.e., spore-containing fungi), the MBP-scFv fusion proteins of Gough et al. failed to provide any anti-fungal benefit for the tomato leaf discs *against* the sporangia.

The Examiner also notes that Gough et al. refer to similar strategies that have been applied to the selection of phage-displayed peptides that bind to the surface of intact platelets. This reference, however, implies that mere peptides would be **inadequate** to accomplish the clearly-stated objectives of Gough et al. (i.e., immunological probes); Gough et al. could have tried this approach, but failed to do so.

Kodadek's methods have nothing to do with the identification of anti-fungal peptides. Instead, Kodadek describes a prokaryotic analog of a conventional two hybrid system, an assay for the detection of peptide-peptide interactions based on a select target molecule, and the identification of genes encoding interactive proteins, for use in affinity purification of the target. The transition from the use of a peptide library in a two-hybrid assay, to the use of the same in vector display methodology (e.g., phage display) directed against an undefined population of unknown targets is not obvious, no more so than any other generalization of what is known (or conjectured) about the specificities of molecular interactions in the field of biochemistry as a whole.

Incredibly, the Examiner asserts that the disclosure of Kodadek, directed to an entirely different assay methodology and use, provides the motivation to substitute peptides into the methods of Gough et al. In addition to describing the disadvantages of antibodies, however, Kodadek also ***discloses similar disadvantages of peptides*** and admits that his early efforts to isolate small peptides using phage display methods not only failed, but "**failed completely**."[8]

Petrenko et al. describe modifications to phage, *per se*, such that the phage will display "global properties" across the entire surface of the phage, independent of the localized properties of the particular displayed peptides, whatever they may be.[9]

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[7] Gough et al. at 107.
[8] Kodadek, page 4, paragraph [0038].
[9] Petrenko et al. at 797.

Petrenko et al. do not disclose any means for identifying anti-fungal peptides. In contrast, claim 1 is directed to the identification of peptides displayed on the surface of a vector that have binding affinity for epitopes displayed on the surface of *Phytophthora*, a goal that does not necessarily involve "global properties" on the surface of the phage. Significantly, claim 1 does not even require that the peptide library be expressed on phage. Instead, the peptide library is expressed on a vector and any vector capable of expressing the peptides of the library may be used.[10]

The Examiner has failed to articulate any basis, grounded in scientific fact and based on the principles of patent law, which would support her finding that a person of ordinary skill in the art would have been led to adopt the method of claim 1 with a reasonable expectation of success. Instead, the Examiner has determined that the Appellants' claimed approach is obvious despite the fact that the cited references disclosed: (i) antibodies that had no anti-fungal effect, (ii) a peptide-based approach that failed completely, and (iii) recombinant phage of general applicability that rely on properties of the phage surface as a whole in single target applications. As such, the Examiner's rejection of claim 1 is nothing more than an impermissible hindsight rejection, using Appellants' disclosure as a template.

C. The Office Has Failed to Articulate a *Prima Facie* Case of Obviousness of the Group II Claims

Claim 9 depends from claim 1 (or 48) and additionally requires that each of the peptides be the same length, the length being 6 to 15 amino acids. Gough et al. describe methods for the isolation of scFv antibodies that bind to the surface of *Phytophthora*. Appellants understand the antibodies of Gough et al. to be substantially longer and more complex than 6- to 15-mer peptides.

According to the Examiner, "the numerous disadvantages cited by appellants above for scFv, would motivate one having ordinary skill in the art to replace the high

[10] See Appellants' Specification, page 11, lines 3-19. Appellants themselves cited Petrenko et al. in their specification as exemplary of particular phage-displayed peptide library that may be used in various embodiments of the invention. See Appellants' Specification, page 11, line 20 to page 12, line 2.

molecular weight scFv fragments with peptides of low molecular weight."[11] However, Kodadek discloses that both random peptides and antibodies are **inadequate** for his purposes, and that phage display methods were not only ineffective in identifying small peptides, they were a **COMPLETE FAILURE**.[12] If anything, the cited references *teach away* from the substitution of 6- to 15-mer peptides for the antibodies of Gough et al. There is simply **no reason** to believe that the substitution of smaller peptides, such as 6- to 15-mers, would even work, let alone provide an improvement over the longer and more complex scFv antibodies of Gough et al.

D. The Office Has Failed to Articulate a *Prima Facie* Case of Obviousness of Claims 44 and 49

Claim 44 depends from claim 1 (or 48) and additionally requires that the library of peptides be an f88-4 peptide library.[13] Random peptide libraries expressed on phage, such as the f88-4 and f8-1 peptide libraries, were known in the art at the time of Appellants' invention. As such, Appellants' specification describes some of the relevant features of these known peptide libraries and provides citations for the relevant art, e.g., Petrenko et al., describing methods for their production.[14]

None of the references cited by Appellants and/or the Office describe the use of the f88-4 and/or f8-1 peptide libraries in connection with *Phytophthora* species, nor do they suggest such uses could be carried out. Significantly, the references cited by Appellants as describing features and methods for the production of the f88-4 and f8-1 phage-displayed peptide libraries pre-date Gough et al. by at least *three years*, yet Gough et al. still selected a phage-**antibody** library of scFv fragments. The Examiner concludes, nonetheless, that the f88-4 and/or f8-1 phage-displayed peptide libraries could be substituted into the methods of Gough et al. Incredibly, the Examiner reaches this conclusion despite the fact that Gough et al.'s method showed no anti-fungal activity

[11] Examiner's Answer dated June 1, 2007, page 17-18.
[12] Kodadek, page 4, paragraph [0038].
[13] Independent claim 49 is similar to claim 1 discussed above and recites that the library of peptides is (1) an f8-1 peptide library, wherein each peptide of the f8-1 peptide library has a length of 8 amino acids, or (2) an f88-4 peptide library, wherein each peptide of the f88-4 peptide library has a length of 15 amino acids.
[14] See Appellants' Specification, page 11, line 20 to page 12, line 2.

and Kodadek said it would not work. There is simply **no reason** to believe that the substitution of the f88-4 and/or the f8-1 peptide libraries would even work, let alone provide an improvement over Gough et al.'s longer and more complex scFv antibodies.

E. The Office Has Failed to Articulate a *Prima Facie* Case of Obviousness of Claim 5

Claim 5 depends from claim 1 discussed above and recites that the sequence of the random oligonucleotide is GCA GNN $(NNN)_7$ or SEQ ID NO: 1.

Smith et al. discuss the use of degenerate oligonucleotides and their use in the production of peptide libraries having synthetic degenerate (i.e., random) oligonucleotides as the insert, a feature that is the very nature of the "random" peptide library.[15] While random oligonucleotides and their use in peptide libraries was known in the art at the time of Appellants' invention, this would not lead a person of ordinary skill to utilize degenerate oligonucleotides in the methods of Gough et al. Further, there is **no reason** to believe that such a substitution would even work, given the respective disclosures of Gough et al., Kodadek, and Petrenko et al.

F. The Office Has Failed to Articulate a *Prima Facie* Case of Obviousness of Claims 35, 36, and 48

Claim 48 recites that the target fungus is selected from the group consisting of *Phytophthora sojae*, *Phytophthora capsici*, *Phytophthora palmivora*, *Phytophthora cinnamomi*, and *Phytophthora parasitica*.

Qui et al. is directed to methods for imparting pathogen resistance to plants by applying a hypersensitive response elicitor peptide *isolated from its corresponding organism* to a plant seed.[16] Qui et al. disclose that their hypersensitive response elicitor peptides may be isolated from such fungal sources as *Phytophthora parasitica*,

[15] Smith et al. at 243-245.
[16] The elicitor-mediated hypersensitive response is a widely distributed pathogen defense mechanism known to occur across a wide variety of plant species in response to bacterial and fungal pathogens. Qui et al. at col. 1, line 18 to col. 6, line 6.

Phytophthora cryptogea, *Phytophthora cinnamomi*, *Phytophthora capsici*, *Phytophthora megasperma*, and *Phytophthora citrophthora*.[17]

The Examiner fails to grasp Qui et al.'s concept. Their focus is on the application of *peptides produced naturally by Phytophthora* and other pathogenic microbes in order to turn on or activate generalized plant resistance mechanisms. In contrast, claim 48 is directed to the identification of *synthetically-produced peptides* (i.e., from the library of peptides prepared from random oligonucleotides) that have affinity for surface factors on *Phytophthora*, some of which will be sufficiently disrupted in function to halt microbe development and pathogenesis. While Qui et al. recite several exemplary *Phytophthora* species as sources for their elicitor polypeptides, this disclosure does not lead to the substitution of various *Phytophthora* species into the methods of Gough et al.

[17] Qui et al. at col. 7, lines 20-23.

G. Conclusion

A *prima facie* case of obviousness has not been established pursuant to 35 U.S.C. § 103 based upon the individual or combined disclosures of Gough et al., Kodadek, Petrenko et al., Smith et al., and Qui et al. It has not been shown that the cited references would have motivated a person of ordinary skill in the art to arrive at Appellants' invention, would have provided a reasonable expectation of success, or when considered as a whole, would have suggested all the requirements of the claimed invention. For these reasons, and those more fully stated above, Appellants respectfully request that the rejections be reversed and claims 1-9 and 32-51 be allowed.

Respectfully submitted,

Edward J. Hejlek, Reg. No. 31,525
SENNIGER POWERS
One Metropolitan Square, 16th Floor
St. Louis, Missouri 63102
(314) 231-5400

EJH/BJS/dep